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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Lloyd G. Mitchell

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08/25/2006

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EXAMINER

EPPS FORD, JANET L

ART UNIT

PAPER NUMBER

1633

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/756,096	<b>Applicant(s)</b> MITCHELL ET AL.	
	<b>Examiner</b> Janet L. Epps-Ford	<b>Art Unit</b> 1633	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

**A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.**

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 6-06-2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 8-26 is/are rejected.
- 7) ☒ Claim(s) 6 and 7 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Claims 1-26 are presently pending for examination, Applicants cancelled claims 27-53 in the amendment filed 6-06-06.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Priority***

3. Applicants have amended the specification to properly state their claim of benefit to US Provisional Application Number 60/008,717 filed on 12-15-1995.

#### ***Specification***

4. Applicant's submission of a statement under 37 CFR 1.125(b) and (c) filed 6/06/06, places the substitute specification filed 12/27/01 in appropriate format for entrance into the record.

#### ***Claim Rejections - 35 USC § 112***

5. The rejection of claims 1-26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in response to Applicant's amendment and arguments.

#### ***Double Patenting***

6. The rejection of claim(s) 1-5, 8-14, 17-19, 22-24, and 26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,013,487, and the rejection of claims 1-26 over claims 1-32 of U.S. Patent No. 6,280,978 B1 are withdrawn in response to Applicant's

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submission of a terminal disclaimer on 6-06-06. However, a new ground of Double Patenting is set forth below.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

### ***Double Patenting***

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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9. Claim(s) 1-5, 8-14, 17-19, 22-24, and 26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,083,702. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims and claims 1-27 of U.S. Patent No. 6,083,072 are both directed to a cell comprising a nucleic acid wherein said nucleic acid comprises one or more target binding domains that target binding of the nucleic acid molecule to a target pre-mRNA expressed within the cell; a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, and methods for producing a chimeric mRNA in a cell, wherein said cell encompasses wherein said cell is in a whole organism. The instant claims are drawn to wherein the nucleic acid molecules comprise a 5' splice donor site, and wherein there is a spacer region that separates the 5' splice donor site and/or the 3' splice site and the 5' splice donor from the target binding domains. This aspect of the instant claims is considered

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an obvious variation of the issued claims, since issued claim 2, limits the nucleic acid of issued claim 1, to comprise a 5' splice donor site. Issued claim 1 comprises one or more target binding domains, a 3' splice region, a branch point, a pyrimidine tract and a 3' splice acceptor site; a spacer region that separates the 3' splice region from the target binding domain; and a nucleotide sequence to be trans-spliced to the target pre-mRNA. Issued claim 2 limits the nucleic acid of claim 1 to further comprise a 5' splice donor site. Although the issued claims do not recite that the issued nucleic acids comprise wherein the 5' splice donor site is separated from the target binding domains by a spacer region, the issued claims are disclosed as "comprising" a 5' splice donor site, therefore separating the 5' splice donor region from the target binding domain by a spacer region would be considered an obvious variation based upon issued claims 2, 9, and 12 which are drawn to a nucleic acid comprising a 5' splice site separated from the target binding domain by a spacer region.

***Claim Rejections - 35 USC § 101***

10. 35 U.S.C. §101 states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 10-18 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter. The term "cell" as defined by the specification at page 25, paragraph [0079] states that the cell is present or intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. Moreover, the following paragraph [00108]

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from page 36 of the specification as filed, clearly teaches that the host cells of the invention are to be incorporated into a host:

The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

#### ***Claim Objections***

11. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

#### ***Claim Rejections - 35 USC § 112***

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 9, recites "***wherein said nucleic acid molecules*** is recognized by nuclear splicing components within the cell." The metes and bounds of this phrase are

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vague and indefinite since claim 1 provides antecedent basis for the phrase "nucleic acid molecule," and not for "nucleic acid *molecules*." It is unclear what other nucleic acid molecules the phrase "*wherein said nucleic acid molecules*" is referring to.

***Claim Rejections - 35 USC § 102***

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Sullenger et al. Sullenger et al. teach a method wherein a chimeric mRNA molecule is produced by interacting a pre-transplicing molecule (PTM) with a target mRNA, wherein the PTM comprises a sequence that binds to the target mRNA, and forms a complex that permits a double splicing event. The target mRNA is spliced such that an AA dinucleotide is removed from the 3' end, the 3'lac region of the PTM is cleaved and added onto the 5'lac of the target sequence (see Figure 1b of Sullenger et al.).

***Claim Rejections - 35 USC § 112***

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 19-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a chimeric mRNA in a cell *in vitro*, does

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not reasonably provide enablement for producing a chimeric mRNA in a human cell *in vivo* for therapeutic treatment of conditions associated with the cystic fibrosis trans-membrane conductance regulator (CFTR) gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record.

18. Applicant's arguments filed 6-06-2006 have been fully considered but they are not persuasive. Applicant traverse the instant rejection on the ground that US Patent No. 6,208,978 dealing with correction of cystic fibrosis by RNA trans-splicing (as here), was clearly found to be enabled.

Contrary to Applicant's assertions, the instant claims are generically drawn to a method for producing a chimeric mRNA comprising contacting a pre-trans-splicing molecule (*of undefined composition*), with a target pre-mRNA, see claim 19. However, the claims in the issued US patent specifically recite the structure of the pre-transplicing molecules. The following is a listing of issued claims 13-15 of US Patent No. 6,208,978.

13. A method of producing a chimeric RNA molecule in a cell comprising:

contacting a target pre-mRNA expressed in the cell with a nucleic acid molecule recognized by nuclear splicing components wherein said nucleic acid molecule comprises:

a) one or more target binding domains that target binding of the nucleic acid molecule to a cystic fibrosis trans-membrane conductance regulator pre-mRNA expressed within the cell;

b) a 3' splice region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site;

c) a spacer region that separates the 3' splice region from the target binding domain; and

d) a nucleotide sequence to be trans-spliced to the target pre-mRNA;

under conditions in which a portion of the nucleic acid molecule is

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trans-spliced to a portion of the target pre-mRNA to form a chimeric RNA within the cell.

14. A method of producing a chimeric RNA molecule in a cell comprising:

contacting a target pre-mRNA expressed in the cell with a nucleic acid molecule recognized by nuclear splicing components wherein said nucleic acid molecule comprises:

a) one or more target binding domains that target binding of the nucleic acid molecule to a cystic fibrosis trans-membrane conductance regulator pre-mRNA expressed within the cell;

b) a 3' splice acceptor site;

c) a spacer region that separates the 3' splice region from the target binding domain; and

d) a nucleotide sequence to be trans-spliced to the target pre-mRNA;

under conditions in which a portion of the nucleic acid molecule is trans-spliced to a portion of the target pre-mRNA to form a chimeric RNA within the cell.

15. A method of producing a chimeric RNA molecule in a cell comprising: contacting a target pre-mRNA expressed within the cell with a nucleic acid molecule recognized by nuclear splicing components wherein said nucleic acid molecule comprises:

a) one or more target binding domains that target binding of the nucleic acid molecule to a cystic fibrosis trans-membrane conductance regulator pre-mRNA expressed within the cell;

b) a 5' splice site;

c) a spacer region that separates the 5' splice site from the target binding domain; and

d) a nucleotide sequence to be trans-spliced to the target pre-mRNA;

wherein a chimeric RNA molecule is produced within the cell.

The instant claims are not limited to the "improvement on the technology," namely wherein the PTM's comprise at least two target binding domains, that applicants describe on page 10 (1<sup>st</sup> full paragraph) of Applicant's response. Therefore, Applicant's arguments are incorrect in regards to the patentability of the instant claims, which are drawn to the use of PTM's of undefined structure, since the features upon which

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Applicant relies upon, namely the present of "at least two target binding domains," are not recited in claims 19-26.

Moreover, in regards to Applicant's reliance upon post-filing data (Liu et al. 2005) to demonstrate the efficacy of the using multi-binding domain PTMs to show correction of the CFTR in CF airways is improper. See MPEP § 2164.05 that states "[T]o overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing." At the time of the instant invention the teachings of Liu et al. (2002 and 2005) was not known the skilled artisan, such that the skilled artisan would have been capable of using (at the time of filing) the claimed methods for treating a disease in a human comprising the administration of vectors which produce the PTMs of the instant invention.

In the instant case, the specification as filed does not provided sufficient guidance and/or instruction that would instruct the skilled artisan regarding how to overcome the known limitations associated with the treatment of cystic fibrosis comprising the use of a gene therapeutic approach as stated above. The quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre-trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. Neither the specification as filed, nor the state of the prior art at the time the invention was made provides any specific guidelines in this regard.

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The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single defective gene is replaced and the desired secondary effect (treating a patient with a disease associated with the expression of the CFTR gene) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

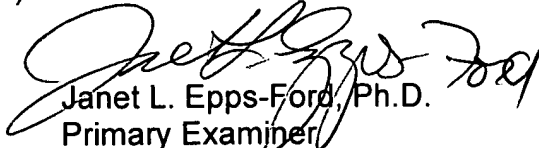
19. Claims 6-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

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20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
Janet L. Epps-Ford, Ph.D.  
Primary Examiner  
Art Unit 1633

JLE